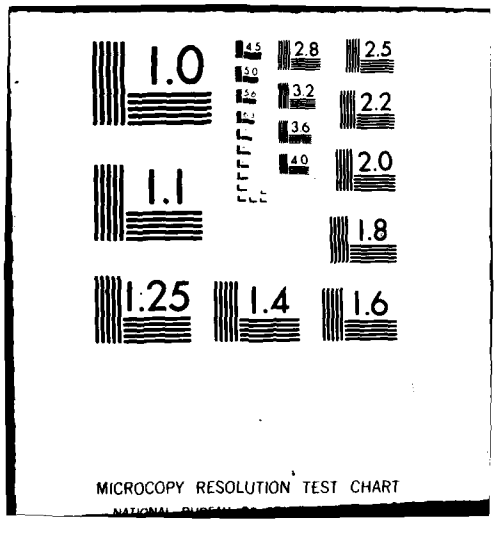
AD-A112 896 LIFE SYSTEMS INC CLEVELAND OH F/G 6/20
MAMMALIAN TOXICOLOGY TESTING: PROBLEM DEFINITION STUDY. ANNUAL --ETC(U)
APR 81 J P GLENNON, R J DAVENPORT DAMD17-81-C-1013
UNCLASSIFIED LSI-TR-477-38A NL

END
DATE FILMED
4-82
DTIC


1.0
1.1
1.25
1.4
1.6
1.8
2.0
2.2
2.5
2.8
3.2
3.6
4.0
4.5
5.0
MICROCOPY RESOLUTION TEST CHART

AD _____

(1)

LSI TR-477-38A

MAMMALIAN TOXICOLOGY TESTING: PROBLEM DEFINITION STUDY

ANNUAL TESTING CAPACITY (U)

by
J. P. Glennon and R. J. Davenport

April, 1981

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701

Contract DAMD17-81-C-1013

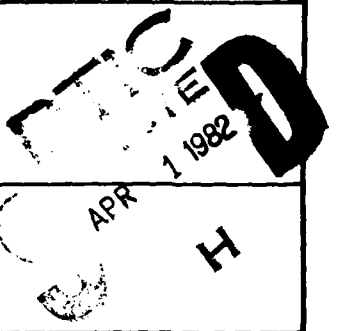
Life Systems, Inc.
Cleveland, OH 44122

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

REPORT DOCUMENTATION PAGE	READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER	2. GOVT ACCESSION NO. AD-A112 896	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) MAMMALIAN TOXICOLOGY TESTING: PROBLEM DEFINITION STUDY, ANNUAL TESTING CAPACITY	5. TYPE OF REPORT & PERIOD COVERED Supporting Document 15 December 1980-5 April 1981
	6. PERFORMING ORG. REPORT NUMBER LSI TR-477-38A
7. AUTHOR(s) J. P. Glennon, R. J. Davenport	8. CONTRACT OR GRANT NUMBER(s) DAMD17-81-C-1013
9. PERFORMING ORGANIZATION NAME AND ADDRESS LIFE SYSTEMS, INC. 24755 Highpoint Road Cleveland, OH 44122	10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS 62777A.3E162777A878.CC.208
11. CONTROLLING OFFICE NAME AND ADDRESS US Army Medical Research and Development Command Fort Detrick Frederick, MD 21701	12. REPORT DATE April, 1981
	13. NUMBER OF PAGES 63
14. MONITORING AGENCY NAME & ADDRESS(if different from Controlling Office)	15. SECURITY CLASS. (of this report) UNCLASSIFIED
	15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

Approved for Public Release; Distribution Unlimited



17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

This report is one of 12 supporting documents to the final reports cited on the reverse side.

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

Mammalian Toxicology Testing, Mammalian Toxicology, Toxicology, Mammalian, Mammalian Toxicology Facility, Toxicology Facility Requirements, Toxicology Testing Capacity, Army Unique Toxicology, Army Toxicology Needs, Toxicology Tests

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

The toxicology testing capacity of a modular Applied Mammalian Toxicology Research/Testing Facility is summarized in this report. Included are individual worksheets that summarize estimates of the maximum allowable testing capacity (number of tests) that could be performed in each Facility module. This information is combined with testing cost data to provide an estimate of the maximum annual operating costs for the Facility.

DD FORM 1 JAN 73 1473 EDITION OF 1 NOV 65 IS OBSOLETE

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

18. continued-

Report Subtitle	Life Systems, Inc. Report Number
Final Reports--	
Part 1. Comparative Analysis Report	LSI-TR-477-2
Part 2. Facility Installation Report	LSI-TR-477-3
Part 3. Impact of Future Changes Report	LSI-TR-477-4

FOREWORD

Reports for this Contract, DAMD17-81-C-1013, consist of three major final reports and twelve supporting documents. The Contract title, MAMMALIAN TOXICOLOGY TESTING: PROBLEM DEFINITION STUDY, is the main title for all the reports. Individual reports are subtitled and referenced with Life Systems, Inc. report numbers as detailed below. Please note that the Life Systems report numbers in test references are shortened. In the Defense Technical Information Center (DTIC) data base the reports are identified by the complete report numbers (i.e., LSI-TR-477-XXX) and complete numbers must be used for retrieval.

Report Subtitle	Life Systems, Inc. Report Number
Final Reports--	
Part 1. Comparative Analysis Report	LSI-TR-477-2
Part 2. Facility Installation Report	LSI-TR-477-3
Part 3. Impact of Future Changes Report	LSI-TR-477-4
Supporting Documents--	
Technology Changes Impact on Testing Requirements	LSI-TR-477-14
Quality Assurance Plan	LSI-TR-477-17A
Capability Modules	LSI-TR-477-19B
Technical Plan	LSI-TR-477-20A
Equipment Plan	LSI-TR-477-21A
Personnel Plan	LSI-TR-477-23A
Inhalation Chambers and Supporting Equipment Survey	LSI-TR-477-26A
Equipment List for Modules	LSI-TR-477-28B
AMTR Protocol/Pricing Report	LSI-TR-477-29A
Global Army Toxicology Requirements	LSI-TR-477-31A
Comparison Toxicology Test Costs	LSI-TR-477-36A
Annual Testing Capacity	LSI-TR-477-38A

SUMMARY

This report provides, under one cover, all of the toxicology testing capacity information related to the modular facility projected for the Army's Applied Mammalian Toxicology Research (AMTR) Program. Included are individual worksheets that summarize estimates of the maximum annual testing capacity (number of tests) that could be performed in each facilty module. This information is combined with testing cost data (developed in TR-477-29) to provide an estimate of the maximum annual operating cost for the facility.

The results of this study indicate the annual operating costs for a facility with one of each toxicity testing module, all operating at maximum capacity would be $32,053,000. If the facility were operated using combined testing protocols for chronic/oncogenic and reproduction/teratogenic studies, the annual operating cost would be $30,649,000.

Conclusion drawn from the study include an estimated annual cost saving of approximately $1.4 million by using combined toxicity testing protocols. It is emphasized that these cost estimates are for a theoretical toxicological facility which contains only one of each type of testing module and that each module is operating at maximum testing capacity. Thus, the estimated annual testing costs represent the "unit" operating costs for the proposed testing facility which require upward modification as additional modules of each type are added. The cost estimates also require downward revision as the deviation from maximum testing capacity is defined for each toxicity test to be performed in the facility.

FOREWORD

The Annual testing capacity estimates described herein were developed by Life Systems, Inc. under U.S. Army Contract DAMD17-81-C-1013 during the period January 6, 1981 to March 20, 1981. The program was directed by Dr. R. A. Wynveen. The technical and administrative efforts were completed by Dr. R. J. Davenport, Dr. J. Glennon, Mrs. D. Jones, Ms. P. Marcinko, Ms. C. D. Patrick, Ms. D. A. Ruschak and Dr. R. A Wynveen.

Col. Allen was the Contracting Officer's Technical Representative for the Letterman Army Institute of Research, San Francisco, CA 94129.

TABLE OF CONTENTS

LIST OF TABLES

INTRODUCTION

A program was undertaken to study and define the Army's requirements for Applied Mammalian Toxicology Research (AMTR) and methods for meeting these requirements. Inherent in the latter is consideration of the types of toxicology testing to be performed, the numbers of tests required and the pricing of this testing. During coordinated efforts other reports have been prepared to define the type and cost of tests to be performed (TR-477-29), describe the module facility for testing (TR-477-19) and develop the Mammalian Toxicology Facility Technical Plan (TR-477-20).

Scope of Document

This document was conceived and prepared to accumulate, under one cover, all of the testing capacity information relative to the modular facility projected for the Army's AMTR Program. Also included is a summary of the annual testing costs assuming that toxicology testing would be performed at maximum module capacity and that there would not be a sharing of modules. A more complete discussion of the impact of this final assumption is provided in the conclusions section of this report.

Objective

The objective of this document is to assemble the testing performance capacity for each test/module combination projected for the Army's AMTR. This document provides estimates of the number of tests that could be performed annually if a single module were included in the new toxicology facilty to perform each specific test. This document also provides documentation of a number of assumptions that had to be made during the early concept stage of the projected toxicology testing facility. The major assumptions required were those dealing with testing protocols where there are no recognized standard testing protocols available. Finally, this document provides a summary of the annual cost for performing toxicology testing in the Army's AMTR under the assumption that all test/module combinations would be utilized at maximum capacity. Recalulation of these operating costs will be required when the Army's specific facility utilization plans are formulated. This is because it would be unlikely that the facility would actually be constructed with "one-each" of each testing module nor that each module would be utilized to its maximum theoretical capacity.

RESULTS

Testing Capacity Analysis

Module Capacity Definition Summary Sheets are provided in Appendix 1 for each toxicology test proposed for the Army's AMTR. A number of assumptions had to be made during this study to develop input data for these worksheets when the information was not available in the literature (e.g., absence of generally acceptable toxicity testing protocols for specific tests). These assumptions as well as those provided by the Principal Investigator at the start of the study are listed in Appendix 2 and Appendix 3, respectively. Finally, a number of errors and omissions in the initial design of the toxicity testing facility were noted during this study. These are listed in Appendix 4.

The annual testing capacity for each toxicity test is summarized in Table 1. This data reflects the number of each test that could be performed per year in the module designed for each specific test. It should be noted that the numbers of tests in this Table probably represent an overstatement of the actual facility's performance characteristics because:

1. There was no accommodation for weekends or holidays in the scheduling of tests.

2. It was assumed that no unusual technical problems would arise during testing to extend the startup time beyond the baseline established for each test, i.e. technical difficulties in generation of aerosols, difficulties in analysis of chamber concentrations, etc.

3. It was assumed that each test would be provided a dedicated module for testing. This overstates the most probable actual testing capacity only where one module is designed for more than one test, e.g. module number 11, (Dermal Testing Area, Rabbit) is used for tests 11, 12, 16 and 17. It is highly unlikely that four number 11 modules would be included in the AMTR to perform each of these tests. At this point in the study, however, the relative distribution of tests to be performed in shared modules is unknown. Thus, it was decided to develop only the maximum testing capacity information shown in Table 1.

A listing of the proposed tests to be performed in the AMTR is included in Table 2 for reference. A listing of modules included in the AMTR is provided in Table 3. Table 4 provides a correlation of modules numbers to test numbers. This provides a ready reference to modules that can be used to support more than one toxicology test. The classification of tests by acute, subchronic and chronic, each cross referenced to test and module number, is provided in Table 5.

Animal Use

Estimates of the numbers of each type of animal that would be required annually to perform testing (at maximum module capacity) is provided in Table 6.

Testing Costs

Cost estimates for performing each type of toxicology test included under this program are summarized in Table 7. Tables 8 and 9 provide the annual costs to perform the principal and special scientific toxicology studies, respectively. Table 10 is a combined summary of these costs. Two total cost values are provided. Using standard toxicology testing protocols, $32,053,000 would be required to perform each type of toxicology test at maximum module capacity (using one dedicated module for each toxicology test). If certain combined protocols were used (combined chronic/oncogenic and reproduction/teratogenic) the annual cost would be $30,649,000. The use of combined testing protocols would provide an annual savings of $1,404,000.

TABLE 1 TESTING CAPACITY SUMMARY

Test No.	Title	Test Duration, D[a]	Module No.	Simultaneous No. of Tests in Module	Module Capacity Tests/Yr.[b]
1	Acute Oral Toxicity Study, Rodent	17	1	36	773
2	Subchronic Oral Tox. Study, Rodent	92	2	4	16
3	Chronic Oral Tox. Study, Rodent	817	3	2	1
4	Acute Inhalation Tox. Study, Rodent	25	5	6	142
5	Subchronic Inhalation Tox. Study, Rodent	100	6	3	11
6	Chronic Inhalation Tox. Study, Rodent	825	7	1	0.4
7	Acute Inhalation Toxicity Study, Primate	25	8	1	24
8	Subchronic Inhalation Tox. Study, Primate	100	9	2	7
9	Chronic Inhalation Toxicity Study, Primate	825	10	1	0.4
10	Subchronic Oral Toxicity Study, Dog	182	4	2	4
11	Acute Dermal Toxicity Study, Rabbit	16	11	7	160
12	Subchronic Dermal Toxicity Study, Rabbit	105	11	8	28
13	Acute Ocular Toxicity Study, Rabbit	14	12	14	365
14	Acute Delayed Neurotoxicity Study, Chicken	24	61	6	91
15	Subchronic Neurotoxicity Study, Chicken	92	61	6	24
16	Acute Dermal Irritation Study, Rabbit	5	11	58	4,234
17	Subchronic Dermal Irritation Study, Rabbit	22	11	8	133
18	Primary Eye Irritation Study, Rabbit	14	12	78	2,033
19	Dermal Sensitization Study, Guinea Pig	39	58	180	1,685
	Special Scientific Toxicology Studies				
S3a	Oncogenic Effects Oral Study, Rodent	902	16[c]	4	2
S3b	Reproductive Effects Study, Rodent	412	18	1	1
S3c	Teratogenic Effects Study, Rodent	37	19	3	30

continued-

(a) Includes preparation and cleanup time.
(b) Rounded to nearest whole number if greater than or nearly equal to 1.0.
(c) Module 16 represents three different oncogenic study areas: rodent oral, rodent inhalation and primate inhalation.

Table 1 - continued

Test No.	Title	Test Duration, D[a]	Module No.	Simultaneous No. of Tests in Module	Module Capacity Tests/Yr.[b]
S3d	Combined Chronic Tox. & Oncogenic Effects Oral Study, Rodent	902	16[c]	2	1
S3e	Combined Reproduction/Teratogenic Effects Study, Rodent	412	18 or 19	1	1
S5	Subchronic Behavioral Effects Inhalation Study, Rodent	100	13[d]	1	4
S6a	Oncogenic Effects Inhalation Study, Rodent	902	16[c]	1	0.4
S6b	Combined Chronic Tox. & Oncogenic Effects Inhaltion Study, Rodent	902	16[c]	1	0.4
S8	Subchronic Behavavioral Effects Inhalation Study, Primate	100	13[d]	1	4
S9a	Oncogenic Effects Inhalation Study, Primate	902	16[c]	1	0.4
S9b	Combined Chronic Tox. & Oncogenic Effects Inhalation Study, Primate	902	16[c]	1	0.4
S20	In Vitro Genetic Toxicity Tests	31	62	3	35
S21	In Vivo Genetic Toxicity Tests	100	63	1	4

(a) Includes preparation and cleanup time.
(b) Rounded to nearest whole number if greater than or nearly equal to 1.0.
(c) Module 16 represents three different oncogenic study areas: rodent oral, rodent inhalation and primate inhalation.
(d) Module contains two testing areas, one for primates (large animals) and one for rodents (other small animals). Capacity based on testing in specified portion of module

TABLE 2 TOXICITY TEST TITLES

Test No.	Test Title[a]
Test No. 1:	Acute Oral Toxicity Study (772.112-21), Rodent
Test No. 2:	Subchronic Oral Toxicity Study (772.112-31), Rodent
Test No. 3:	Chronic Oral Toxicity Study (772.113-3), Rodent
Special Test No. 3: (S3a)	Oncogenic Effects Oral Study (772.113-2), Rodent
Special Test No. 3: (S3b)	Reproductive Effects Study (772.116-3), Rodent
Special Test No. 3: (S3c)	Teratogenic Effects Study (772.116-2), Rodent
Special Test No. 3: (S3d)	Combined Chronic Toxicity and Oncogenic Effects Oral Study, Rodent
Special Test No. 3: (S3e)	Combined Reproduction/Teratogenic Effects Study, Rodent
Test No. 4:	Acute Inhalation Toxicity Study (772.112-23), Rodent
Test No. 5:	Subchronic Inhalation Toxicity Study (772.112-33), Rodent
Special Test No. 5: (S5)	Subchronic Behavioral Effects Inhalation Study, Rodent
Test No. 6:	Chronic Inhalation Toxicity Study (772.113-3), Rodent
Special Test No. 6: (S6a)	Oncogenic Effects Inhalation Study (772.113-2), Rodent
Special Test No. 6: (S6b)	Combined Chronic Toxicity and Oncogenic Effects Inhalation Study, Rodent
Test No. 7:	Acute Inhalation Toxicity Study, Primate
Test No. 8:	Subchronic Inhalation Toxicity Study, Primate
Special Test No. 8: (S8)	Subchronic Behavioral Effects Inhalation Study, Primate
Test No. 9:	Chronic Inhalation Toxicity Study (772.113-3), Primate

continued-

(a) Federal Register publication reference numbers provided in parentheses when available.

Table 2 - continued

Test No.	Test Title[a]
Special Test No. 9: (S9a)	Oncogenic Effects Inhalation Study (772.113-2), Primate
Special Test No. 9: (S9b)	Combined Chronic Toxicity and Oncogenic Effects Inhalation Study, Primate
Test No. 10:	Subchronic Oral Toxicity Study (772.112-31), Dog
Test No. 11:	Acute Dermal Toxicity Study (772.112-22), Rabbit
Test No. 12:	Subchronic Dermal Toxicity Study, Rabbit
Test No. 13:	Acute Ocular Toxicity Study, Rabbit
Test No. 14:	Acute Delayed Neurotoxicity Study (163.81-7), Chicken
Test No. 15:	Subchronic Neurotoxicity Study (163.82-5), Chicken
Test No. 16:	Acute Dermal Irritation Study (772.112-25), Rabbit
Test No. 17:	Subchronic Dermal Irritation Study, Rabbit
Test No. 18:	Primary Eye Irritation Study (772.112-24), Rabbit
Test No. 19:	Dermal Sensitization Study (772.112-26), Guinea Pig
Special Test No. 20:	*In Vitro* Genetic Toxicity Tests
Special Test No. 21:	*In Vivo* Genetic Toxicity Tests

(a) Federal Register publication reference numbers provided in parentheses when available.

TABLE 3 LIST OF MODULES

No.	Title
1.	Acute Oral Exposure Area, Rodent
2.	Subchronic Oral Exposure Area, Rodent
3.	Chronic Oral Exposure Area, Rodent
4.	Subchronic Oral Exposure Area, Dog
5.	Acute Inhalation Exposure Area, Rodent
6.	Subchronic Inhalation Exposure Area, Rodent
7.	Chronic Inhalation Exposure Area, Rodent
8.	Acute Inhalation Exposure Area, Primate
9.	Subchronic Inhalation Exposure Area, Primate
10.	Chronic Inhalation Exposure Area, Primate
11.	Dermal Testing Area, Rabbit
12.	Ocular Testing Area, Rabbit
13.	Behavioral Studies Area
14.	Metabolism/Pharmacokinetics Studies Area
15.	Pharmacodynamics Studies Area
16.	Oncogenic Studies Area
17.	Respiratory Physiology Studies Area
18.	Reproduction Studies Area
19.	Teratology Studies Area
20.	Food Preparation/Blending Area
21.	Non-radioactive Waste Handling/Disposal Area
22.	Refrigerated Food Stroage Area
23.	Quality Assurance Laboratory
24.	Animal Quarantine Area
25.	Pathology Laboratory
26.	Clinical Chemistry Laboratory
27.	Animal Breeding Area
28.	Veterinary Medicine Area
29.	Analytical/Synthetic Chemistry Laboratory
30.	Automated Data Processing Area
31.	Radiochemistry Laboratory
32.	Cage/Rack Washing and Storage Area
33.	Chemical Storage Area
34.	Showers, Lockers and Toilets Area
35.	Glassware Washing Area
36.	Library Area
37.	Technical Offices Area
38.	Shipping and Receiving Area
39.	Luncheon Room Area
40.	Record Archives Area
41.	Specimen Storage Area
42.	Linen Storage Area
43.	Janitorial Storage Area
44.	Central Cylinder Gas Storage Area
45.	Equipment Maintenance Area
46.	Laundry Area
47.	Central Power Area

continued-

Table 3 - continued

No.	Title
48.	Central Standby (Emergency) Power Area
49.	Central Water Supply Conditioning Area
50.	Central Wastewater Conditioning Area
51.	Central Air Handling Area
52.	Central Heating Area
53.	Central Compressed Air/Vacuum Area
54.	Central Communications Area
55.	Central Refrigeration Area
56.	Central Toilet Area
57.	Central Vacuum Cleaning Area
58.	Dermal Testing Area, Rodent
59.	Central Automated Facility Systems Control Area
60.	Administrative Office Area
61.	Neurotoxicology Studies Area, Chicken
62.	In Vitro Genetic Toxicology Studies Area
63.	In Vivo Genetic Toxicology Studies Area

TABLE 4 MODULE/TEST CORRELATION

Module No.	Test No.	Number of Test per Year per Module[a]
1	1	773
2	2	16
3	3	1
4	10	4
5	4	142
6	5	11
7	6	0.4
8	7	24
9	8	7
10	9	0.4
11	11	160
	12	28
	16	4,234
	17	133
12	13	365
	18	2,033
13	S5	4
	S8	4
16	S3a	2
	S3d	1
	S6a	0.4
	S6b	0.4
	S9a	0.4
	S9b	0.4
18	S3b	1
	S3e	1
19	S3c	30
58	19	1,685
61	14	91
	15	24
62	S20	35
63	S21	4

(a) Rounded to nearest whole number except when significantly less than 1.

TABLE 5 TOXICOLOGY TEST DISTRIBUTION

Test Duration	Route of Exposure	Animal	Test Number	Module Number
Acute	Oral	Rodent	1	1
		Chicken	14	61
	Dermal	Guinea Pig	19	58
		Rabbit	11	11
		Rabbit	16	11
	Ocular	Rabbit	13	12
		Rabbit	18	12
	Inhalation	Rodent	4	5
		Primate	7	8
Subchronic	Oral	Rodent	2	2
		Dog	10	4
		Chicken	15	61
	Dermal	Rabbit	12	11
		Rabbit	17	11
	Inhalation	Rodent	5	6
		Rodent	S5	13
		Primate	8	9
		Primate	S8a	13
Chronic	Oral	Rodent	3	3
		Rodent	S3a	16
		Rodent	S3b	19
		Rodent	S3c	18
		Rodent	S3d	16
		Rodent	S3e	19
	Inhalation	Rodent	6	7
		Rodent	S6a	16
		Rodent	S6b	16
		Primate	9	10
		Primate	S9a	16
		Primate	S9b	16
Screening (Genetic Studies)	Variable	Bacteria Mammalian Cells Drosophila	S20	62
Subchronic (Genetic Studies)	Variable	Rodent	S21	63

TABLE 6 RATE OF ANIMAL USE AT MAXIMUM CAPACITY

Test No.	Animal	Number per Test	Maximum Number Tests per Module per Year	Maximum Number of Animals per Module per Year
1	Rodent[a]	50	772.9	38,645
2	Rodent	320	15.9	5,088
3	Rodent	880	0.9	792
4	Rodent	50	141.8	7,090
5	Rodent	200	11.0	2,200
6	Rodent	880	0.4	352
7	Primate[b]	50	23.6	1,180
8	Primate	80	7.3	584
9	Primate	80	0.4	32
10	Dog	48	4.0	192
11	Rabbit	100	159.7	15,970
12	Rabbit	80	27.8	2,224
13	Rabbit	50	365.0	18,250
14	Chicken	60	91.3	5,478
15	Chicken	60	23.8	1,428
16	Rabbit	12	4234.0	50,808
17	Rabbit	80	132.7	10,616
18	Rabbit	9	2033.0	18,297
19	Guinea Pig	10	1684.6	16,846
	Special Scientific Toxicology Studies			
S3a	Rodent	480	1.6	768
S3b	Rodent	120	0.9	108
S3c	Rodent	100	29.6	2,960
S3d	Rodent	880	0.9	792
S3e	Rodent	120	0.9	108
S5	Rodent	30	3.7	111
S6a	Rodent	480	0.4	192
S6b	Rodent	880	0.4	352
S8	Primate	6	3.7	22
S9a	Primate	80	0.4	32
S9b	Primate	80	0.4	32

(a) Assume rat for all tests with rodents
(b) Assume monkey for all tests with primates

TABLE 7 MAMMALIAN TOXICOLOGY TEST PRICE LIST (3/8/81)

Test No.	Duration	Type of Animal	Route of Exposure	Price, $(000) Per Outcome[a]							
					Special Scientific Toxicology Studies[b]						
										Combined Protocols	
				General Toxicology[c]	Behavioral	Onco-genic	Repro-duction	Terato-genic	Neuro-toxi-cology	Gen. Tox. + Oncog.	Repro./ Terato.
1	Acute	Rodent[d]	Oral	2.4[e]	—	—	—	—	—	—	—
2	Subchronic	Rodent[d]	Oral	56[e]	—	—	—	—	—	—	—
3	Chronic	Rodent[d]	Oral	495[e]	—	377[e]	114[e]	27[e]	—	600[f]	125[f]
4	Acute	Rodent[d]	Inhalation	5.0[e]	—	—	—	—	—	—	—
5	Subchronic	Rodent[d]	Inhalation	64[e]	100[f]	—	—	—	—	—	—
6	Chronic	Rodent[d]	Inhalation	613[e]	—	515[f]	—	—	—	1000[f]	—
7	Acute	Primate	Inhalation	39[f]	—	—	—	—	—	—	—
8	Subchronic	Primate	Inhalation	196[f]	150[f]	—	—	—	—	—	—
9	Chronic	Primate	Inhalation	518[f]	—	420[f]	—	—	—	800[f]	—
10	Subchronic	Dog	Oral	104[e]	—	—	—	—	—	—	—
11	Acute	Rabbit	Dermal	4.2[e]	—	—	—	—	—	—	—
12	Subchronic	Rabbit	Dermal	75[g]	—	—	—	—	—	—	—
13	Acute	Rabbit	Ocular	2.5[f]	—	—	—	—	—	—	—
14	Acute	Chicken	Oral	—	—	—	—	—	5.4[e]	—	—
15	Subchronic	Chicken	Oral	—	—	—	—	—	20[e]	—	—
				Irritation	Sensitization						
16	Acute	Rabbit	Dermal	0.7[e]	—						
17	Subchronic	Rabbit	Dermal	3.0[g]	—						
18	Acute	Rabbit	Ocular	0.9[e]	—						
19	Acute	Guinea Pig	Dermal	—	3.9[e]						

(a) Rounded off to nearest $1,000 for prices in excess of $5,000. Assumes one species.
(b) Special Scientific Toxicology Studies: Metabolism/Pharmacokinetics, Pharmacodynamics, and Respiratory are deleted since they are not a part of the 19 tests.
(c) General Toxicology includes lethality, metabolism and pharmacokinetics/pharmocodynamics.
(d) Rodent studies price was based on use of the rat.
(e) SOURCE: Enviro Control, Inc. 1980, Cost Analysis Methodology & Protocol Estimates. TSCA Health Standards and FIFRA Guidelines. Rockville, MD: Enviro Control, Inc. U.S. Environmental Protection Agency.
(f) Price estimated by LSI since no quotable source was identified.
(g) SOURCE: ICF, Inc. 1980. Profile of the Chemical Safety Testing Industry: An Assessment of Pesticide Testing Capacity. Final Report. Washington, DC: ICF, Inc. U.S. Environmental Protection Agency.

TABLE 8 ANNUAL COST AT MAXIMUM TESTING CAPACITY: PRINCIPAL TOXICOLOGY STUDIES[a]

Test No.	Maximum No. Tests per Module per Year	Cost per Test, $ (000)	Maximum Cost per Module per Year, $ (000)
1	772.9	2.4	1,855
2(b)	15.9	56.0	890
3(b)	0.9	495.0	446
4	141.8	50.0	7,090
5(b)	11.0	64.0	704
6(b)	0.4	613.0	245
7	23.6	39.0	920
8(b)	7.3	196.0	78
9(b)	0.4	518.0	207
10	4.0	104.0	416
11	159.7	4.2	671
12	27.8	75.0	2,085
13	365.0	2.5	913
14	91.3	5.4	493
15	23.8	20.0	476
16	4234.0	0.7	2,962
17	132.7	3.0	398
18	2033.0	0.9	1,830
19	1684.6	3.9	6,570
		Total	29,249

(a) Assume separate module dedicated to each test.
(b) Deleted if combined protocols performed.

TABLE 9 ANNUAL COST AT MAXIMUM TESTING CAPACITY: SPECIAL SCIENTIFIC TOXICOLOGY STUDIES[a]

Test No.	Maximum No. Tests per Module per Year	Cost per Test, $ (000)	Maximum Cost per Module per Year, $ (000)
Single-Study Protocols			
S3a[b]	1.6	377	603
S3b[b]	0.9	114	103
S3c[b]	29.6	27	799
S5	3.7	100	370
S6a[b]	0.4	515	206
S8	3.7	150	555
S9a[b]	0.4	420	168
		Total	2,804
Combined Protocols			
S3d	0.9	600	540
S3e	0.9	125	113
S6b	0.4	1,000	400
S9b	0.4	800	320
		Total	1,373

(a) Separate breakout for combined protocols that would be performed as substitutes for other principal and special scientific toxicology studies.
(b) Deleted if combined protocols performed.

TABLE 10 SUMMARY OF ANNUAL COST AT MAXIMUM CAPACITY[a]

Item	Annual Cost, $(000)
1. Cost of Principal Toxicology Studies (Tests 1-19)	29,249
2. Cost of Special Scientific Studies (not including Combined Protocols)	2,804
3. Total annual cost of testing at maximum module capacity (Item 1 plus Item 2)	32,053
4. Cost of Combined Protocols (Tests S3d, S3e, S6b and S9b)	1,373
5. Cost of tests deleted when Combined Protocols are used (Tests 3, S3a, S3b, S3c, 6, S6a, 9 & S9a)	2,777
6. Cost saving by using Combined Protocols (Item 5 minus Item 4)	1,404
7. Total annual cost of testing at maximum module capacity using Combined Protocols (Item 3 minus Item 6)	30,649

(a) Does not include Genetic Toxicology Studies (Tests S20 and S21)

CONCLUSIONS

The information contained in this report provides the basic data necessary for calculating the testing capacity and annual operating cost for the Army's AMTR. The actual operating costs for that toxicology testing facility will be determined after the Army's specific toxicology testing program for the AMTR has been formulated. The most critical decision to be made will be the number of each type of module to be included in the final testing facility. This will be a function of the number of each type of test that is desired. Once the number of modules in the final facility are determined, the actual annual testing capacity and operating cost can then be more accurately estimated.

In this regard, it is again emphasized that the testing capacity values and estimated annual cost contained herein, do not necessary reflect the actual values likely for the Army's AMTR. These values reflect LSI's estimate if only one module were included in the facility to support each specific toxicology test. In reality some significant differences will be present in the ultimate facility. Some tests, required on a low frequency basis and/or of short duration, will be performed together in the same or highly similar testing module. For example, tests 11, 12, 16 and 17 can all be performed in module 11, either concurrently or in sequence. It is also likely that more than one of each module designed for chronic studies will be included in the AMTR. For example, the Army may desire a testing capability to perform more than one rodent oncogenic study every two years as would be the case in a facility with only one number 16 module for rodents.

REFERENCES

Enviro Control, Inc. 1980. Cost analysis methodology and protocol estimates, TSCA health standards and FIFRA guidelines. Draft report. Rockville, MD: Enviro Control, Inc., U.S. Environmental Protection Agency.

Fribush S., Langer G., ICF, Inc. 1980. Profile of the chemical safety testing industry: an assessment of pesticide testing capacity. Final report. Washington, DC: ICF, Inc., U.S. Environmental Protection Agency contract no. WA78-B247.

APPENDIX 1

MODULE CAPACITY DEFINITIONS

Test No.: 1
Test Title: Acute Oral Toxicity Study, Rodent

Module No.: 1
Module Title: Acute Oral Exposure Area, Rodent

MODULE CAPACITY DEFINITION

Specification	Value	Parameter	Reference
1. Time for setup, test and cleanup, D:	17	T	
• Time for test, D	15		
• Time for setup and cleanup, D	2		
2. Number of animals per test:(a)	50	A	772.112-21 (TR-477-29, pp. A1-3)
• No. per sex per group	5/2/5		
3. Number of animals per module:	1,800	M	
• Cages per rack	30		
• Animals per cage	5		
• Racks per module	12		
4. Capacity of module for simultaneous tests:	36	C°	

$$C = \frac{M}{A} = \frac{1800}{50} = 36$$

$$C° = 36$$

where C° = Rounded-down capacity, per general assumption to avoid splitting tests among modules

5. Number of tests per year:	772.9	N	

$$N = \frac{365}{T} (C°)$$

$$N = 21.47 \times 36 = 772.9$$

(a) Control plus 4 dose groups.

Test No.: 2
Test Title: Subchronic Oral Toxicity Study, Rodent

Module No.: 2
Module Title: Subchronic Oral Exposure Area, Rodent

MODULE CAPACITY DEFINITION

Specification	Value	Parameter	Reference
1. Time for setup, test and cleanup, D:	92	T	
• Time for test, D	90		
• Time for setup and cleanup, D	2		
2. Number of animals per test:(a)	320	A	772.112-31 (TR-477-29, pp. A1-4)
• No. per sex per group(a)	40/2/4		
3. Number of animals per module:	1,800	M	
• Cages per rack	30		
• Animals per cage	5		
• Racks per module	12		
4. Capacity of module for simultaneous tests:	4	C°	

$$C = \frac{M}{A} = 5.6$$

$$C° = 4$$

where C° = Rounded-down capacity, per general assumption to avoid splitting tests among modules or splitting subchronic/chronic tests among rooms

5. Number of tests per year:	15.9	N	

$$N = \frac{365}{T} (C°)$$

$$N = 15.9$$

(a) Control plus 3 dose groups.

Test No.: 3
Test Title: Chronic Oral Toxicity Study, Rodent

Module No.: 3
Module Title: Chronic Oral Exposure Area, Rodent

MODULE CAPACITY DEFINITION

Specification	Value	Parameter	Reference
1. Time for setup, test and cleanup, D:	817	T	
• Time for test, D	815		
• Time for setup and cleanup, D	2		
2. Number of animals per test:(a)	880	A	772.113-2 (TR-477-29, pp. A1-7)
• No. per sex per group	110/2/4		
3. Number of animals per module:	1,800	M	
• Cages per rack	30		
• Animals per cage	5		
• Racks per module	12		
4. Capacity of module for simultaneous tests:	2	C°	

$$C = \frac{M}{A} = 2.0$$

$$C^\circ = 2.0$$

where C° = Rounded-down capacity, per general assumption to avoid splitting tests among modules

5. Number of tests per year:	0.9	N	

$$N = \frac{365}{T} (C^\circ)$$

$$N = 0.9$$

(a) Control plus 3 dose groups.

Special Test No.: 3 (S3a)
Test Title: Oncogenic Effects Oral Study, Rodent

Module No.: 16
Module Title: Oncogenic Studies Area

MODULE CAPACITY DEFINITION

Specification	Value	Parameter	Reference
1. Time for setup, test and cleanup, D:	902	T	
• Time for test, D	900		
• Time for setup and cleanup, D	2		
2. Number of animals per test:[a]	480	A	772.113-2 (TR-477-29, pp. A1-11)
• No. per sex per group	60/2/4		
3. Number of animals per module:	1,800 (1920)[b]	M	
• Cages per rack	30		
• Animals per cage	5		
• Racks per module	12		
4. Capacity of module for simultaneous tests:	4	C°	

$C = \frac{M}{A} = 4.0$

$C° = 4.0$

where C° = Rounded-down capacity, per general assumption to avoid splitting tests among modules or rooms

5. Number of tests per year:	1.6	N	

$N = \frac{365}{T} (C°)$

$N = 1.6$

(a) Control plus 3 dose groups.
(b) Additional 30 rats added/room to permit one study per room.

Special Test No.: 3(S3b)
Test Title: Reproductive Effects Study, Rodent

Module No.: 18
Module Title: Reproduction Studies Area

MODULE CAPACITY DEFINITION

Specification	Value	Parameter	Reference
1. Time for setup, test and cleanup, D:	412	T	
• Time for test, D	410		
• Time for setup and cleanup, D	2		
2. Number of animals per test:	120/400[b]	A	772.116-3 (TR-477-29, pp. A1-14)
• No. per group[a]	30/4		
3. Number of animals per module:	450	M	
• Cages per rack	30		
• Animals per cage	5		
• Racks per module	3		
4. Capacity of module for simultaneous tests:	1.0	C	

$$C = \frac{M}{A} = \frac{4500}{400} = 1.1$$

$$C^\circ = 1.0$$

where C° = Rounded-down capacity, per general assumption to avoid splitting tests among modules or among rooms for major tests

5. Number of tests per year:	0.9	N	

$$N = \frac{365}{T} (C^\circ)$$

$$N = 0.9$$

(a) Control plus 3 dose groups, 20 females and 10 males/group at start.
(b) May be in excess of 400 animals per test at specific times during study.

Special Test No.: 3(S3c)
Test Title: Teratogenic Effects Study, Rodent

Module No.: 19
Module Title: Teratology Studies Area

MODULE CAPACITY DEFINITION

Specification	Value	Parameter	Reference
1. Time for setup, test and cleanup, D:	37	T	
• Time for test, D	35		
• Time for setup and cleanup, D	2		
2. Number of animals per test:(a)	100	A	772.116-2 (TR-477-29, pp. A1-16)
• No. per sex per group	20/1/5		
3. Number of animals per module:	450	M	
• Cages per rack	30		
• Animals per cage	5		
• Racks per module	3		
4. Capacity of module for simultaneous tests:	36	C°	

$$C = \frac{M}{A} = \frac{450}{100} = 4.5$$

$$C° = 3.0$$

where C° = Rounded-down capacity, per general assumption to avoid splitting tests among modules or among racks

5. Number of tests per year:	29.6	N	

$$N = \frac{365}{T} (C°)$$

$$N = 29.6$$

(a) Two controls plus 3 dose groups (positive and vehicle or sham controls).

Special Test No.: 3(S3d)
Test Title: Combined Chronic Toxicity and Oncogenic Effects Oral Study, Rodent

Module No.: 16
Module Title: Chronic Oral Exposure Area, Rodent

MODULE CAPACITY DEFINITION

1. No specific calculation performed for module capacity due to uncertainty in unique nature for such special study protocols.

2. Assume will be similar to Test No. 3 (Chronic Effects) where N = 0.9

Special Test No.: 3(S3e)
Test Title: Combined Reproduction/Teratogenic Effects Study, Rodent

Module No.: 18 or 19
Module Title: Reproduction or Teratology Studies Area

MODULE CAPACITY DEFINITION

1. No specific calculation performed for module capacity due to uncertainty in unique study protocol.

2. Assume will be similar to Test No. 3 (S3b) (Reproductive Effects), N = 0.9

Test No.: 4
Test Title: Acute Inhalation Toxicity Study, Rodent

Module No.: 5
Module Title: Acute Inhalation Exposure Area, Rodent

MODULE CAPACITY DEFINITION

Specification	Value	Parameter	Reference
1. Time for setup, test and cleanup, D:	25	T	
• Time for test, D	15		
• Time for setup and cleanup, D	10		
2. Number of animals per test:(a)	50	A	772.112-23 (TR-477-29, pp. A1-20)
• No. per sex per group	5/2/5		
3. Number of exposures per day per chamber:	1	E	
4. No of chambers per module:	8	G	
5. No. of tests per every 11 days:	6	C°	

$$C = (E)\frac{\text{4 doses per chamber}}{\text{No. of groups per test}}(G)$$

$$C = 1(4/5)(8) = 6.4$$

$$C° = 6.0$$

where C° = Rounded-down to prevent fractional tests each time period

6. Number of animals exposed:		M	
• Per day of exposure	300		
• Per 14 day observation period	600 max		
7. Capacity of holding area:	2,700	H	
• No. of racks	18		
• No. of cages per rack	30		
• No. of animals per cage	5		
8. No of tests per year:	141.8	N	

$$N = \frac{\text{1 exposure day}}{\text{11 days}}(C°)\ (52\ \text{weeks/yr})(5\ \text{days/week})$$

$$N = \frac{C°(260)}{11} = 141.8$$

9. H must be equal or slightly greater than M.

(a) Control plus 4 dose groups.

Test No.: 5
Test Title: Subchronic Inhalation Toxicity Study, Rodent

Module No.: 6
Module Title: Subchronic Inhalation Exposure Area, Rodent

MODULE CAPACITY DEFINITION

Specification	Value	Parameter	Reference
1. Time for setup, test and cleanup, D:	100	T	
• Time for test, D	90		
• Time for setup and cleanup, D	10		
2. Number of animals per test:(a)	200	A	772.112-33 (TR-477-29, pp. A1-22)
• No. per sex per group(a)	25/2/4		
3. Number of exposures per day per chamber:	1(b)	E	
4. Number of animals exposed per day:	600		
5. Capacity of holding area:	900	H	
• No. of racks	6		
• No. of cages per rack	30		
• No. of animals per cage	5		
6. No. of chambers per module:	12	G	
7. No. of tests per 100 days:	3	C	
8. No. of tests per year:	11	N	

$$N = \frac{365}{100}(C) = 11.0$$

9. H must be equal to or slightly greater than M.

(a) Control plus 3 dose groups.
(b) Six hours per day, five days per week; or continuous.

Test No.: 5(S5)
Test Title: Subchronic Behavioral Effects Inhalation Study, Rodent

Module No.: 13
Module Title: Behavioral Studies Area

MODULE CAPACITY DEFINITION

Specification	Value	Parameter	Reference
1. Time for setup, test and cleanup, D:	100	T	
• Time for test, D	90		
• Time for setup and cleanup, D	10		
2. Number of animals per test:[(a)]	30	A	
• No. per sex per group[(a)]	10/1/3		Assumption
3. Number of exposures per day per chamber:	1	E	
4. Number of animals exposed per day:	30	M	
5. Capacity of holding area:	90	H	
• No. of racks	3		
• No. of cages per rack	30		
• No. of animals per cage	1		
6. No. of chambers per module:	3	G	
7. No. of tests per 100 days:	1	C	
8. No. of tests per year:	3.7	N	

$$N = \frac{365}{100} (C) = 3.7$$

9. H must be greater than or equal to M.

(a) Control plus 2 dose groups.

Test No.: 6
Test Title: Chronic Inhalation Toxicity Study, Rodent

Module No.: 7
Module Title: Chronic Inhalation Exposure Area, Rodent

MODULE CAPACITY DEFINITION

Specification	Value	Parameter	Reference
1. Time for setup, test and cleanup, D:	825	T	
• Time for test, D	815		
• Time for setup and cleanup, D	10		
2. Number of animals per test:(a)	880	A	772.113-3 (TR-477-29, pp. A1-27)
• No. per sex per group	110/2/4		
3. Number of exposures per day per chamber:	1(b)	E	
4. Number of animals exposed per day:	880	M	
5. Capacity of holding area:	1200	H	
• No. of racks	8		
• No. of cages per rack	30		
• No. of animals per cage	5		
6. No. of chambers per module:	4	G	
7. No. of tests per 825 days:	1	C	
8. No. of tests per year:	0.4	N	

$$N = \frac{365}{825}(C) = 0.4$$

9. H must be equal to or slightly greater than M.

(a) Control plus 3 dose groups.
(b) Six hours per day, five days per week; or continuous.

Special Test No.: 6(S6a)
Test Title: Oncogenic Effects Inhalation Study, Rodent

Module No.: 16
Module Title: Oncogenic Studies Area

MODULE CAPACITY DEFINITION

1. No specific calculation performed for module capacity due to uncertainty in study design.

2. Assume will be similar to Test No. 6, N = 0.4

Special Test No.: 6(S6b)
Test Title: Combined Chronic Toxicity and Oncogenic Effects Inhalation Study, Rodent

Module No.: 16
Module Title: Oncogenic Studies Area

MODULE CAPACITY DEFINITION

1. No specific calculation performed for module capacity due to uncertainty in protocol design.

2. Assume will be similar to Test No. 6, N = 0.4

Test No.: 7
Test Title: Acute Inhalation Toxicity Study, Primate

Module No.: 8
Module Title: Acute Inhalation Exposure Area, Primate

MODULE CAPACITY DEFINITION

Specification	Value	Parameter	Reference
1. Time for setup, test and cleanup, D:	25	T	
• Time for test, D	15		
• Time for setup and cleanup, D	10		
2. Number of animals per test:(a)	50	A	Assume similar to rodent protocol, 772.112-23 (TR-477-29, pp. A1-20)
• No. per sex per group	5/2/4		
3. Number of exposures per day per chamber:	1	E	
4. Number of chambers per module:	5	G	
5. No. of tests per day:	1	C	
$C = (E)\frac{\text{1 dose per chamber}}{\text{No. of groups per test}}(G)$			
6. Number of animals exposed:			
• Per day of exposure	50		
• Per 14 day observation period	100 max	M	
7. Capacity of holding area:	144	H	
• No. of racks	6		
• No. of cages per rack	24		
• No. of animals per cage	1		
8. No. of tests per year:	23.6	N	

$$N = \left(\frac{\text{1 exposure}}{\text{11 days}}\right)(C)(52\ \text{weeks/yr})(5\ \text{days/week})$$

$$N = \frac{C(260)}{11} = 23.6$$

9. H must be equal to or slightly greater than M.

(a) Control plus 3 dose groups.

Test No.: 8
Test Title: Subchronic Inhalation Toxicity Study, Primate

Module No.: 9
Module Title: Subchronic Inhalation Exposure Area, Primate

MODULE CAPACITY DEFINITION

Specification	Value	Parameter	Reference
1. Time for setup, test and cleanup, D:	100	T	
• Time for test, D	90		
• Time for setup and cleanup, D	10		
2. Number of animals per test:	80	A	Assume similar to rodent protocol, 772.112-33 (TR-477-29, pp. A1-22)
• No. per sex per group[a]	10/2/4		
3. Number of exposures per day per chamber:	1[b]	E	
4. Number of animals exposed per day:	80	M	
5. Capacity of holding area:	N/A[c]	H	
• No. of racks	N/A		
• No. of cages per rack	N/A		
• No. of animals per cage	N/A		
6. No. of chambers per module:	8	G	
7. No. of tests per 100 days:	2	C	
• No. animales per chamber	20		
• No. chamber per test	4		
8. No. of tests per year:	7.3	N	

$$N = \frac{365}{100}(C) = 7.3$$

(a) Control plus 3 dose groups.
(b) Six hours per day, five days per week.
(c) NA = Not Applicable (inhalation chambers are also used for holding).

Test No.: 8 (S8)
Test Title: Subchronic Behavioral Effects Inhalation Study, Primate

Module No.: 13
Module Title: Behavioral Studies Area

MODULE CAPACITY DEFINITION

Specification	Value	Parameter	Reference
1. Time for setup, test and cleanup, D:	100	T	
• Time for test, D	90		
• Time for setup and cleanup, D	10		
2. Number of animals per test:	6	A	Assumption (TR-477-29, pp. A1-37)
• No. per sex per group[a]	2/1/3		
3. Number of exposures per day per chamber:	2	E	
4. Number of animals exposed per day:	4[b]		
5. Capacity of holding area:	6	H	
• No. of racks	1		
• No. of cages per rack	6		
• No. of animals per cage	1		
6. No. of chambers per module:	2	G	
7. No. of tests per 100 days:	1	C	
8. No. of tests per year:	3.7	N	

$$N = \frac{365}{100} = 3.7$$

(a) Control plus 2 dose groups.
(b) Controls not exposed in chamber.

Test No.: 9
Test Title: Chronic Inhalation Study, Primate

Module No.: 10
Module Title: Chronic Inhalation Exposure Area, Primate

MODULE CAPACITY DEFINITION

Specification	Value	Parameter	Reference
1. Time for setup, test and cleanup, D:	825	T	
• Time for test, D	815		
• Time for setup and cleanup, D	10		
2. Number of animals per test:	80	A	Assume protocol same as sub-chronic except for duration (See Test 8)
• No. per sex per group[a]	10/2/4		
3. Number of exposures per day per chamber:	1[b]	E	
4. Number of animals exposed per day:	80		
• No. aminals per chamber	20		
5. Capacity of holding area:	N/A[c]	H	
• No. of racks	N/A		
• No. of cages per rack	N/A		
• No. of animals per cage	N/A		
6. No. of chambers per module:	4	G	
7. No. of tests per 825 days:	1	C	
8. No. of tests per year:	0.4	N	

$$N = \frac{365}{825}(C) = 0.4$$

(a) Control plus 3 dose groups.
(b) Six hours per day, five days per week; or continuous.
(c) NA = Not Applicable (inhalation chambers are also used for holding).

Special Test No.: 9(S9a)
Test Title: Oncogenic Effects Inhalation Study, Primate

Module No.: 16
Module Title: Oncogenic Studies Area,

MODULE CAPACITY DEFINITION

1. No specific calculation performed for module capacity.

2. Assume will be similar to Test No. 9, N = 0.4

Special Test No.: 9(S9b)
Test Title: Combined Chronic Toxicitiy and Oncogenic Effects Inhalation Study, Primate

Module No.: 16
Module Title: Oncogenic Studies Area

MODULE CAPACITY DEFINITION

1. No specific calculation performed for module capacity.

2. Assume will be similar to Test No. 9, N = 0.4

Test No.: 10
Test Title: Subchronic Oral Toxicity Study, Dog

Module No.: 4
Module Title: Subchronic Oral Exposure Area, Dog

MODULE CAPACITY DEFINITION

Specification	Value	Parameter	Reference
1. Time for setup, test and cleanup, D:	182	T	
• Time for test, D	180		
• Time for setup and cleanup, D	2		
2. Number of animals per test:(a)	48	A	772.112-31 (TR-477-29, pp. A1-46)
• No. per sex per group	6/2/4		
3. Number of animals per module:	120	M	
• Runs per layer	1		
• Animals per run	2		
• Runs per module	60		
4. Capacity of module for simultaneous tests:	2.0	C°	

$$C = \frac{M}{A} = \frac{120}{48} = 2.5$$

$$C° = 2.0$$

where C° = Rounded-down capacity, per general assumption to avoid splitting tests among modules

5. Number of tests per year:	4.0	N	

$$N = \frac{365}{T} (C°)$$

$$N = 4.0$$

(a) Control plus 3 dose groups.

Test No.: 11
Test Title: Acute Dermal Toxicity Study, Rabbit

Module No.: 11
Module Title: Dermal Testing Area, Rabbit

MODULE CAPACITY DEFINITION

Specification	Value	Parameter	Reference
1. Time for setup, test and cleanup, D:	16	T	
• Time for test, D	15		
• Time for setup and cleanup, D	1		
2. Number of animals per test:(a)	100	A	772.112-22 (TR-477-29, pp. A1-49)
• No. per sex per group	5/2/10		
3. Number of animals per module:	704	M	
• Cages per rack	32		
• Animals per cage	1		
• Racks per module	22		
4. Capacity of module for simultaneous tests:	7.0	C°	

$$C = \frac{M}{A} = 7.04$$

$$C° = 7.0$$

where C° = Rounded-down capacity, per general assumption to avoid splitting tests among modules

5. Number of tests per year:	159.7	N	

$$N = \frac{365}{T} (C°)$$

$$N = 159.7$$

(a) Control plus 4 dose groups for abraded and non-abraded animals, i.e., total of 10 groups.

Test No.: 12
Test Title: Subchronic Dermal Toxicity Study, Rabbit

Module No.: 11
Module Title: Dermal Testing Area, Rabbit

MODULE CAPACITY DEFINITION

Specification	Value	Parameter	Reference
1. Time for setup, test and cleanup, D:	105	T	
• Time for test, D	104		
• Time for setup and cleanup, D	1		
2. Number of animals per test:(a)	80	A	Assumpition, similar to rodent oral protocol, (TR-477-29, pp. A1-4)
• No. per sex per group	10/2/4		
3. Number of animals per module:	704	M	
• Cages per rack	32		
• Animals per cage	1		
• Racks per module	22		
4. Capacity of module for simultaneous tests:	8	C°	

$$C = \frac{M}{A} = 8.8$$

$$C° = 8.0$$

where C° = Rounded-down capacity, per general assumption to avoid splitting tests among modules

5. Number of tests per year:	27.8	N	

$$N = \frac{365}{T} (C°)$$

$$N = 27.8$$

(a) Control plus 3 dose groups.

Test No.: 13
Test Title: Acute Ocular Toxicity Study, Rabbit

Module No.: 12
Module Title: Ocular Testing Area, Rabbit

MODULE CAPACITY DEFINITION

Specification	Value	Parameter	Reference
1. Time for setup, test and cleanup, D:	14	T	
• Time for test, D	13		
• Time for setup and cleanup, D	1		
2. Number of animals per test:(a)	50	A	Assumpition, similar to rodent oral protocol, (TR-477-29, pp. A1-3)
• No. per sex per group	5/2/5		
3. Number of animals per module:	704	M	
• Cages per rack	32		
• Animals per cage	1		
• Racks per module	22		
4. Capacity of module for simultaneous tests:	14	C°	

$$C = \frac{M}{A} = 14.1$$

$$C° = 14$$

where C° = Rounded-down capacity, per general assumption to avoid splitting tests among modules

5. Number of tests per year:	365	N	

$$N = \frac{365}{T} (C°)$$

$$N = 365$$

(a) Control plus 4 dose groups.

Test No.: 14
Test Title: Acute Delayed Neurotoxicity Study, Chicken

Module No.: 61
Module Title: Neurotoxicology Studies Area, Chicken

MODULE CAPACITY DEFINITION

Specification	Value	Parameter	Reference
1. Time for setup, test and cleanup, D:	24	T	
• Time for test, D	22		
• Time for setup and cleanup, D	2		
2. Number of Animals per test:(a)	60	A	163.81-7 (TR-477-29, pp. A1-52)
• No. per sex per group	20/1/3		
3. Number of animals per module:	384	M	
• Cages per rack	32		
• Animals per cage	1		
• Racks per module	12		
4. Capacity of module for simultaneous tests:	6	C°	

$$C = \frac{M}{A} = \frac{384}{60} = 6.4$$

$$C° = 6$$

where C° = Rounded-down capacity, per general assumption to avoid splitting tests among modules

5. Number of tests per year:	91.3	N	

$$N = \frac{365}{T} (C°)$$

$$N = 91.3$$

(a) Two controls plus 1 dose groups (positive control and vehicle control).

Test No.: 15
Test Title: Subchronic Neurotoxicity Study, Chicken

Module No.: 61
Module Title: Neurotoxicology Studies Area, Chicken

MODULE CAPACITY DEFINITION

Specification	Value	Parameter	Reference
1. Time for setup, test and cleanup, D:	92	T	
• Time for test, D	90		
• Time for setup and cleanup, D	2		
2. Number of animals per test:(a)	60	A	163.82-5 (TR-477-29, pp. A1-54)
• No. per sex per group	10/1/6		
3. Number of animals per module:	384	M	
• Cages per rack	32		
• Animals per cage	1		
• Racks per module	12		
4. Capacity of module for simultaneous tests:	6	C°	

$$C = \frac{M}{A} = \frac{384}{60} = 6.4$$

$$C° = 6$$

where C° = Rounded-down capacity, per general assumption to avoid splitting tests among modules

5. Number of tests per year:	23.8	N	

$$N = \frac{365}{T} (C°)$$

$$N = 23.8$$

(a) 3 controls plus 3 dose groups (positive, negative and vehicle controls).

Test No.: 16
Test Title: Acute Dermal Irritation Study, Rabbit

Module No.: 11
Module Title: Dermal Testing Area, Area, Rabbit

MODULE CAPACITY DEFINITION

Specification	Value	Parameter	Reference
1. Time for setup, test and cleanup, D:	5	T	
• Time for test, D	4		
• Time for setup and cleanup, D	1		
2. Number of animals per test:(a)	12	A	772.112-25 (TR-477-29, pp. A1-56)
• No. per sex per group	6/1/2		
3. Number of animals per module:	704	M	
• Cages per rack	32		
• Animals per cage	1		
• Racks per module	22		
4. Capacity of module for simultaneous tests:	58	C°	

$$C = \frac{M}{A} = 58.7$$

$$C° = 58$$

where C° = Rounded-down capacity, per general assumption to avoid splitting tests among modules

5. Number of tests per year:	4,234	N	

$$N = \frac{365}{T} (C°)$$

$$N = 4,234$$

(a) Vehicle control plus 1 dose group (males or females can be used).

Test No.: 17
Test Title: Subchronic Dermal Irritation Study, Rabbit

Module No.: 11
Module Title: Dermal Testing Area, Rabbit

MODULE CAPACITY DEFINITION

Specification	Value	Parameter	Reference
1. Time for setup, test and cleanup, D:	22	T	
• Time for test, D	21		
• Time for setup and cleanup, D	1		
2. Number of animals per test:(a)	80	A	Assumption (TR-477-29, pp. A1-57)
• No. per sex per group	5/2/8		
3. Number of animals per module:	704	M	
• Cages per rack	32		
• Animals per cage	1		
• Racks per module	22		
4. Capacity of module for simultaneous tests:	8.0	C°	

$C = \frac{M}{A} = 8.8$

$C° = 8.0$

where C° = Rounded-down capacity, per general assumption to avoid splitting tests among modules

5. Number of tests per year:	132.7	N	

$N = \frac{365}{T} (C°)$

$N = 132.7$

(a) Control plus 3 dose groups for abraded and non-abraded.

Test No.: 18
Test Title: Primary Eye Irritation Study, Rabbit

Module No.: 12
Module Title: Ocular Testing Area, Rabbit

MODULE CAPACITY DEFINITION

Specification	Value	Parameter	Reference
1. Time for setup, test and cleanup, D:	14	T	
• Time for test, D	13		
• Time for setup and cleanup, D	1		
2. Number of animals per test:(a)	9	A	772.112-24 (TR-477-29, pp. A1-58)
• No. per sex per group	9/1/1		
3. Number of animals per module:	704	M	
• Cages per rack	32		
• Animals per cage	1		
• Racks per module	22		
4. Capacity of module for simultaneous tests:	78	C°	

$C = \frac{M}{A} = 78.2$

$C° = 78.0$

where C° = Rounded-down capacity, per general assumption to avoid splitting tests among modules

5. Number of tests per year:	2,033	N	

$N = \frac{365}{T} (C°)$

$N = 2,033$

(a) One dose group, serves as own control.

Test No.: 19
Test Title: Dermal Sensitization Study, Guinea Pig

Module No.: 58
Module Title: Dermal Testing Area, Rodent

MODULE CAPACITY DEFINITION

Specification	Value	Parameter	Reference
1. Time for setup, test and cleanup, D:	39	T	
• Time for test, D	38		
• Time for setup and cleanup, D	1		
2. Number of animals per test:	10	A	772.112-26
• No. per sex per group[a]	10/1/1		(TR-477-29, pp. A1-59)
3. Number of animals per module:	1,800	M	
• Cages per rack	30		
• Animals per cage	5		
• Racks per module	12		
4. Capacity of module for simultaneous tests:	180	C°	

$$C = \frac{M}{A} = 180$$

$$C° = 180$$

where C° = Rounded-down capacity, per general assumption to avoid splitting tests among modules

5. Number of tests per year:	1,684.6	N	

$$N = \frac{365}{T} (C°)$$

$$N = 1,684.6$$

(a) One dose group, serves as own control.

Special Test No.: 20 (S20)
Test Title: In Vitro Genetic Toxicity Tests[a]

Module No.: 62
Module Title: In Vitro Genetics Toxicology Studies Area

MODULE CAPACITY DEFINITION

Specification	Value	Parameter	Reference
1. Time for setup, test and cleanup, D:	31	T	Assumption
• Time for test, D	30		
• Time for setup and cleanup, D	1		
2. Capacity of module for simultaneous tests:	3[b]	C	Assumption
3. Number of tests per year:	35.3	N	

$$N = \frac{365}{T} (C)$$

$$N = 35.3$$

(a) Includes all non-animal genetics tests in Drosophila, bacteria and mammalian cell cultures.
(b) Capacity based more on size of staff than facility.

Special Test No.: 21(S21)
Test Title: In Vivo Genetics Toxicity Tests, Rodents[a]

Module No.: 63
Module Title: In Vivo Genetics Toxicology Studies Area

MODULE CAPACITY DEFINITION

Specification	Value	Parameter	Reference
1. Time for setup, test and cleanup, D:	100	T	Assumption
• Time for test, D	90		
• Time for setup and cleanup, D	10		
2. Number of animals per module:	900	M	
• Cages per rack	30		
• Animals per cage	5		
• Racks per module	6		
3. Numbers of animals per battery of tests:	900[b]	A	Assumption
4. Capacity of module for simultaneous battery of tests:	1[b]	C	
$C = \frac{M}{A}$			
$C = 1$			
5. Number of tests per year:	3.7	N	
$N = \frac{365}{T}\ (C°)$			
$N = 3.7$			

(a) Includes: Mouse specific locus test, in vivo cytogenic tests, dominant lethal test, heritable translocation assay.
(b) Assume one module dedicated to mutagenicity testing and unique combination of tests (test battery) required on chemical will not exceed module capacity.

APPENDIX 2 ASSUMPTIONS MADE DURING STUDY

1. Where modules could contain whole tests plus fractional tests, it is assumed that the fraction of a test would not be performed in order to keep all animals exposed to the test chemical in the same module. Multiple tests in the same module will be performed in separate rooms within the module except for acute studies. Tests will not be split between rooms within a module.

2. Chicken cage assumed to be 1.5' x 1.5' x 1.5' in size. In 6' x 3' x 6' rack, 32 cages held with one animal per cage.

3. Rabbit cage assumed to be 1.5' x 1.5' x 1.5' in size. In 6' x 3 ' x 6' rack, 32 cages held with one animal per cage.

4. In test S3a, it is assumed that best utilization of facilities will provide for adding an extra 30 animals (six cages) to each room within the module in order to keep each test confined to a single room.

5. For test S3b, the test assumed to start with 120 animals, but may increase to more than 400 at a later date. It goes through two reproductive generations.

6. Test No. 13 (Acute Ocular Toxicity Study, Rabbit) uses same protocol as Test No. 11 (Acute Dermal Toxicity Study, Rabbit) except that (because abraided and unabraided animals are not needed) only 50 animals are required per test.

7. Facilities required for Guinea Pig assumed to be same as for rat.

8. Acute inhalation chambers for rodents are assumed to be designed for four levels exposure simultaneously. Therefore, each chamber in module can expose four dose groups at the same time.

9. Assume in rodent acute inhalation study, Test No. 4, five animals per dose.

10. Acute inhalation primate test (No. 7) is based on protocol for acute inhalation, rodent.

11. Primate inhalation tests based on monkeys, not baboons.

12. Assume protocol for chronic inhalation study with primates (No. 9) is based on Test No. 5, for rodents.

13. Behavioral studies in rodent and primate (Tests No. S5 and S8, respectively) assume:

    a. Primate test uses approximately 1/4 number of animals used in rodent test.
    b. Can use males or females.
    c. Control and two doses
        - Rodents 10/1/3
        - Primates 2/1/3

d. Primates may be monkeys or baboons.
e. Two exposures per day, can do four animals (baboons only) per day using two chambers.
f. Primate control not placed in chamber.

APPENDIX 3

ASSUMPTIONS PROVIDED AT START OF STUDY

1. There will be 18 mammalian toxicology tests plus genetic toxicology testing. See the attached table for the 18 types of tests. (The number of tests changed during course of this study.)

2. View the assignment as dividing the work into rodents, primates, rabbits, dogs and chickens. Recognize, however, that no module has been incorporated for chickens. This was an oversight in the modules selected. Would like a plan, however, for how many chickens might be under test in the way of chemicals.

3. The capacity should be viewed as testing capacity as opposed to full-service toxicology capability capacity. The latter includes consulting, literature searches, protocol preparation, criteria doucment reviews, etc., all which occurs prior to the actual testing.

4. I have a table of the Genetic Toxicology tests.

5. An assumption will have to be made to determine what quantity of teratology studies, reproduction studies, behavioral studies, etc, have to be done. See the attached organizational location chart which shows the types of toxicology testing/research to be done.

APPENDIX 4

INITIAL MODULE DESIGN ERRORS AND OMISSIONS

1.	Module 4:	No information on number of dogs per run or number of runs per layer. LSI assumed one run per layer, two animals per run.
2.	Tests (dogs):	No testing capacility has been identified for acute dog studies, i.e., oral LD50 in dog. Such a study would generally be needed to determine requirement for and dose levels during 90-day dog study (Test 10).
3.	Tests (chickens):	Omitted both acute and subchronic oral testing areas.
4.	Tests (primates, inhalation):	Inhalation chambers (6' x 6' x 11') will not fit in the walk-in hoods illustrated (8.5' x 4' x unk.).
5.	Holding areas in acute inhalation areas:	Greatly oversized.

DISTRIBUTION LIST

USAMRDC (SGRD-RMS)
Fort Detrick
Frederick, MD 21701

Defense Technical Information Center (DTIC)
ATTN: DTIC-DDA
Cameron Station
Alexandria, VA 22314